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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,569	07/16/2002	Takashi Muramatsu	SPO-116	7190

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

EXAMINER	
HARRIS, ALANA M	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,569	MURAMATSU ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/09/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: ___.

DETAILED ACTION

Response to Amendments and Arguments

1. Claims 1-16 are pending.

Claims 10-12, drawn to non-elected inventions are withdrawn from examination.

Claims 1, 8, 9 and 13 have been amended.

Claims 15 and 16 have been added.

Claims 1-9 and 13-16 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on December 9, 2002 as Paper number 12 was reviewed and the documents therein were considered by the Examiner. A copy of the signed PTO-1449 accompanies this Final Rejection.

Specification

4. Applicants have amended the title, which is clearly indicative of the invention.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

5. The rejection of claims 1-9, 13 and 14 under 35 U.S.C. 112, second paragraph, set forth in the First Action on the Merits (FAOM) in paragraph 8, sections a and c as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicants' amendments.

Claim Rejections - 35 USC § 102

6. The rejection of claims 1-7, 13 and 14 under 35 U.S.C. 102(b) as being anticipated by Tsutsui et al (Cancer Research 53:1281-1285, March 15, 1993/ Reference R7 from IDS, Paper number 12) is withdrawn.

7. The rejection of claims 1 and 13 under 35 U.S.C. 102(b) as being anticipated by Nakagawara et al. (Cancer Research 55(8): 1792-1797, April 15, 1995/ Reference R1 from IDS, Paper number 9) is withdrawn.

8. The rejection of claims 1-9, 13 and 14 under 35 U.S.C. 102(a) as being anticipated by Ikematsu et al. (British Journal of Cancer 83(6): 701-706, September 2000/ Reference R3 from IDS, Paper number 12) is withdrawn because this reference was not publicly available until September 12, 2000.

9. The rejection of claims 1-5, 9, 13 and 14 under 35 U.S.C. 102(b) as being anticipated by Aridome et al. (Jpn. J. Cancer Res. 86: 655-661, 1995/ Reference R1 from IDS, Paper number 12) is withdrawn.

10. The rejection of claim 13 under 35 U.S.C. 102(b) as being anticipated by Ye et al. (British Journal of Cancer 79(1): 179-184, January 1999/ Reference R2 from IDS Paper number 9) is withdrawn.

Claim Rejections - 35 USC § 103

11. The rejection of claims 1-9, 13 and 14 under 35 U.S.C. 103(a) as being unpatentable over Tsutsui et al (Cancer Research 53:1281-1285, March 15, 1993/ Reference R7 from IDS, Paper number 12), in view of Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12) is withdrawn.

12. The rejection of claims 1-5, 8, 9, 13 and 14 under 35 U.S.C. 103(a) as being unpatentable over Aridome et al. (Jpn. J. Cancer Res. 86: 655-661, 1995/ Reference R1 from IDS, Paper number 12), in view of Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12) is withdrawn.

Maintained Rejections and New Grounds of Rejection

Claim Rejections - 35 USC § 112

13. Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Applicants have amended claim 13 to include method steps not supported by the specification. Applicants have included the recitations "...before and after treatment using a one-step sandwich enzyme immunoassay,"; "comparing the level measured after treatment to a level measured before treatment,"; and "wherein a reduction...after treatment is indicative of successful therapy and positive prognosis". In the Remarks received on the 28th of November 2003 Applicants have not specified by page and line number where in the specification support for these recitations and methods steps are listed. A review of the specification by the Examiner has not resulted in finding support. Applicants are requested to pointedly express where support is or delete the new matter. If the new matter is deleted the 102(b) rejection of Ye and 112, second paragraph, section c set forth in the FAOM will be reinstated.

14. The rejection of claims 1-9, 13, 14 and newly added claims 15 and 16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

Applicants assert that human midkine is known in the art and references several documents. Applicants also aver that the human midkine protein lacking an N-domain is known in the art and an article by Kaname et al. (Biochem. Biophys. Res. Commun. 219: 256-260, 1996) demonstrates this midkine mutant. Furthermore, Applicants state, "the genus claimed in the amended claims does not have substantial variation. These arguments have been carefully considered, but found unpersuasive.

Applicants have not provided sufficient evidence clearly demonstrating that there is only one known human midkine sequence. Applicants rely on references that did not accompany the remarks of November 28, 2003. The Examiner did review U.S. Patent number 5,461,029 (October 24, 1995), but this one reference cannot be relied upon as an authority on the instant matter. Notwithstanding, Applicants' specification notes that midkine includes not only a full-length MK protein, a fragment comprising an amino acid sequence of any length and mutants, see bridging paragraph of pages 4 and 5. It is not clear if the Kaname reference addresses the same mutant midkine as the mutant midkine suggested by Applicants. Applicants continually do not provide sufficient evidence that there is only one human midkine protein with an amino acid sequence well known in the art. Likewise, Applicants vaguely suggests a domain near the N terminus is missing from the human midkine, however do not explicitly detail what amino acid residues are lacking from the sequence.

As set forth in the FAOM Applicants are not required to disclose every species encompassed by a genus, however there needs to be a sufficient description of a representative number of species by actual reduction to practice. "A 'representative

number of species' means that the species which are adequately described are representative of the entire genus." "Adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only species within the genus", see Official Gazette, column 1, 1242: 174, January 30, 2001. For the reasons of record and set forth the rejection is maintained.

There is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph.

15. The rejection of claims 1-9, 13, 14 and newly added claims 15 and 16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting cancer and assessing cancer prognosis comprising the steps of measuring the level of human midkine protein in a biological sample, does not reasonably provide enablement for a method for detecting cancer and assessing cancer prognosis comprising the measuring the level of a midkine mutant or a midkine fragment is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants argue that the amendments to the claims render the instant enablement rejection moot. Applicants continue to rely on their specification and a

reference that has not been provided. These points of view have been fully considered but found unpersuasive.

The Examiner has noted that the specification evidences a method of measuring the serum MK level in hepatocellular carcinoma and gastric cancer patients at stages I to IV in Figures 1-8. Figures 9 and 10 exemplify a method of measuring the urine MK level from colon, hepatocellular and gastric cancer patients and correlations were made between urine MK values in cancer patients and cancer stages, see corresponding captions on page 13, lines 9-20. These examples seem to exemplify Applicants use of an antibody that recognized human full-length MK (not defined by an amino acid sequence or sequence identifier) and not mutants and arbitrary fragments of MK. The specification does not provide enabling disclosure that evidences a method for detecting cancer comprising measuring a midkine mutant lacking a domain near the N terminus, which is ultimately a fragment of MK, implementing the said method with an antibody that recognizes the said mutant or a method of assessing cancer prognosis using the said fragments and undefined mutant and variant MK molecules before and after treatment. The specification nor Remarks provide sufficient guidance as to which of the amino acids may be changed in mutant MK of arbitrary amino acid length while MK structural or functional activity and specificity is retained. Without such guidance, the changes, which can be made in the MK amino acids, still maintain biological activity or structural specificity of MK molecules by MK antibodies is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

16. The rejection of claims 1-9, 13, 14 and newly added claims 15 and 16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are maintained and made.

a. Claims 1, 2, 4, 6 and 9 are vague and indefinite in the recitation "early cancer". Applicants pointedly express that page 4, lines 16-28 of the specification set forth the definition of "early cancer". This section notes that "[e]arly cancer includes stage 0 (carcinoma in situ) and stage 1 according to the TNM classification." That statement in itself does not preclude other stages or clearly differentiates between a "normal" person without cancer, who is also symptomless and a person who is deemed as having early cancer. The term "early" continues to not aid in classifying or staging the cancer.

b. The recitation "a one-step sandwich enzyme immunoassay" in claims 1, 13, 15 and 16 is vague and indefinite. The Examiner has reviewed Example 2, which according to Applicants is a one-step sandwich method, see pages 14 and 15. However, as the methodology is listed the assays seems to involve a multiplicity of steps, therefore it is not clear what Applicants intend to mean by *one-step* sandwich method.

c. The recitation "a domain near the N terminus" in claims 1, 9 and 13 is vague and indefinite. This recitation does not clear describe what type of domain or what amino acid residues are removed form the human midkine protein. Accordingly, the metes and bounds cannot be determined.

d. Claim 13 is vague and indefinite in the recitations, "treatment", "successful therapy and positive prognosis". It is not clear what type of treatment is being administered. Nor is it clear what type of therapy is regarded as successful and likewise what prognosis is regarded as positive. Is successful therapy indicated by the subject not incurring nausea or additional sickness, little or no pain or complete remission of cancer? Furthermore, is a positive prognosis regarded as no metastasis of the primary cancer, ensured greater quality of life, or increased life span? The metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 102

17. Claims 1-8, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Song et al. (Biomedical Research 18(5): 375-381, 1997). Song discloses a method for measuring a human midkine (MK) protein in sera from patients with early stage gastric, hepatocellular and lung cancer, see pages 376-378. Normal human serum MK was compared with the MK level of the cancer patients, see page 375, column 2, section before Materials and Methods section. Several case numbers are assigned to the different cancers, as well as the status of the cancer. Quite a few within each organ system were denoted as having no detection of metastasis and interpreted by the Examiner as reading on an early stage cancer, see page 376, Table 1; page 377, Figure legend. Detection and measure of MK was conducted with an enzyme-linked immunoassay using a pair of antibodies, see page 375, column 2, Materials and Methods section.

Given the broadest interpretation it is reasonable to conclude that "treatment" encompasses surgery. Song discloses MK level measurement before and after treatment, see page 377, column 2, Serum MK section; and page 378, Figure 1.

18. The rejection of claims 1 and 9 under 35 U.S.C. 102(b) as being anticipated by Ye et al. (British Journal of Cancer 79(1): 179-184, January 1999/ Reference R2 from IDS Paper number 9) is maintained.

Applicants traverse the instant rejection with the assertion that their assay is "...highly advantageous for the detection of early cancer...". This point of view has been carefully considered, but found unpersuasive.

Applicants have not set forth convincing arguments relative to inferred differences between the assays of Ye and the claimed invention. For the reasons of record the rejection is maintained.

18. The rejection of claims 1, 4, 5, 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12) is maintained.

Applicants argue that Muramatsu does not describe detection of "early" cancer and does not suggest the one-step sandwich enzyme assay. Applicants further aver that Muramatsu does not disclose any weaknesses or deficiencies of the anticipatory method. These arguments and points of view have been considered, but found unpersuasive.

Patients of the anticipatory method of Muramatsu had hepatocellular carcinoma. The paper did not disclose that it was metastatic or abrogated the liver, hence this cancer is regarded as an early cancer, confined to the site of development and reads on Applicants' claims. Absent any evidence to the contrary these carcinomas were limited to the liver. The assay method disclosed in the bridging paragraph of columns 1 and 2 on page 1172 and the enzyme-linked immunoassay (EIA) described in column 2 of page 1172 is the same as Applicants' method, see "Determination of MK Levels..." section starting on page 1173. Applicants have not explicitly pointed out differences in the methods. Given the endpoint of both methods are the same, comparing the level of human midkine protein between a cancerous sample and control sample Muramatsu continues to anticipates the claims. And lastly Applicants' claims do not read on listing any weaknesses or deficiencies, notwithstanding Muramatsu anticipates the claimed invention for the reasons of record.

Claim Rejections - 35 USC § 103

19. Claims 1-8, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song et al. (Biomedical Research 18(5): 375-381, 1997). The teachings of Song have been presented in the 102(b) rejection. Song does not teach the anticipatory method, wherein the level of a human midkine protein that lacks a domain near the N terminus is measured.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to implement a comparative analysis before

and after a method of cancer treatment detecting a "...MK devoid of the N terminal domain has been so far detected only in tumor specimens but not in adjacent non-cancerous tissues", see page 379, column 2. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success to assay the truncated MK since "[b]oth the serum MK level and the truncated MK mRNA in cancerous tissue may be used as tumor markers", see bridging paragraph of pages 379 and 380; and particularly page 380, column 1, last sentence.

20. Claims 1, 9 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ye et al. (British Journal of Cancer 79(1): 179-184, January 1999/ Reference R2 from IDS Paper number 9). The teachings of Ye have been presented and reiterated above. Ye does not teach the anticipated method wherein the level of human midkine protein is measured before, as well as after treatment and correlating the difference in the measure levels to determine successful therapy and positive prognosis.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to implement a comparative analysis before and after a method of cancer treatment because a health practitioner would need to make a determination of whether the mode of treatment was indeed effective. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success to monitor the patient's expression of a tumor marker in determining the effectiveness of the treatment modality in an effort to determine the

patient's prognosis, as well as enhancing the ability of a physician to change and/or optimize therapy.

21. Claims 1, 4, 5, 8, 9 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12). The teachings of Muramatsu have been presented and reiterated above. Ye does not teach the anticipated method wherein the level of human midkine protein is measured before, as well as after treatment and correlating the difference in the measure levels to determine successful therapy and positive prognosis.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to implement a comparative analysis before and after a method of cancer treatment because a health practitioner would need to make a determination of whether the mode of treatment was indeed effective. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success to monitor the patient's expression of a tumor marker in determining the effectiveness of the treatment modality in an effort to determine the patient's prognosis, as well as enhancing the ability of a physician to change and/or optimize therapy.

Conclusion

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571) 272-0831. The examiner can normally be reached on 7:00 am to 4:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne "Bonnie" Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
4 March 2004